Biologics in peri-operative management of Crohn's disease

S. B. Hanauer

University of Chicago Hospital, Department of Gastroenterology, University of Chicago Pritzker School of Medicine, Chicago, U.S.A.

Abstract

The role of biologics for peri-operative Crohn's disease will remain speculative until the accumulation of clinical trial data. The potential positioning of peri-operative biologic therapies includes the prevention of surgery, minimizing surgical morbidity or prevention or delaying post-operative disease recurrence. To date, there is limited, indirect data regarding the potential for infliximab to prevent surgery via the effective treatment of refractory disease and the improvement in fistulizing disease. Although there is no controlled data regarding the impact of biologics on surgical morbidity, patients with stricturing disease have undergone resection without added morbidity. Post-operative trials are certainly needed to ascertain the impact on the inevitability of disease recurrence. (Acta gastroenterol. belg., **2001**, 64, **191-192**).

The question as to the role of biologics in the peri-operative management of Crohn's disease will be a matter for speculation until an evidence base has been created. However, until such time we can begin to develop a framework for the clinical approach as to how biologics should be considered to impact upon the peri-operative course of Crohn's disease. Three relevant positions for peri-operative therapy would include preventing an indication for surgery, minimizing surgical morbidity, and preventing or delaying post-operative disease recurrence.

Indications for surgery in Crohn's disease are primarily directed at treating complications of the chronic inflammatory disease process. These include : obstruction (due to fibrostenoses), strategic fistulae, hemorrhage, neoplasia and to treat refractory disease. Traditional therapies have not had a demonstrable impact on disease complications such as obstruction or fistulization although corticosteroids can transiently relieve inflammatory obstructions and fistula drainage can be reduced by the use of antibiotics or cyclosporine. No therapy, to date, (short of surgical resection) has reduced the potential for dysplasia or cancer in Crohn's disease. Therefore, if biologic therapy can alter the natural history of Crohn's disease by preventing complications such as obstruction or fistulization, then a pre-operative role would be to prevent surgery.

The prevention of surgery has been, at least, relatively accomplished by the ability of infliximab to induce clinical improvement in patients who had not been responsive to prior medical therapy with corticosteroids, aminosalicylates or immune suppressants (1,2) and to treat fistula (3). Whether these effects are transient or long-term have yet to be addressed but the benefits of therapy targeted at TNF have had demonstrable clinical as well as mucosal (4) and histological (5) effects. Additional, outcome data suggest that infliximab has reduced hospitalization rates for Crohn's disease (R. Cohen, personal communication).

In contrast, there are no data that infliximab or other biologics *prevent* fistulae or obstruction (6). Along these lines, there is an undercurrent of speculation that fibrostenotic complications may increase after treatment with infliximab as several patients in controlled trials and post-marketing experience have developed obstructions after or during treatment with infliximab. These observations must be interpreted with caution due to concurrent events such as the reduction in steroids that typically result from clinical improvements with infliximab.

There is even less data regarding the role of biologic therapy to influence the acute or long-term post-surgical course of Crohn's disease. While surgeons have reported anecdotes regarding "ease of surgery" after infliximab treatment, there are no strong data to define whether post-surgical morbidity is reduced with pre-surgical therapy. Nevertheless, it is intuitive that reduced bowel inflammation could lead to more facile dissection, the ability to limit resected margins thus preserving intestine, and a lower risk of anastomotic breakdown. Again, these speculations must be modified by the potential role for TNF and other inflammatory mediators in wound healing.

Finally, the issue of reducing or delaying post-operative recurrence would be a worthy goal for biologic strategies. To date, the benefits of mesalazine have been less apparent than first anticipated (7) and neither antibiotic therapy nor immunomodulators have been "optimized" to define more (or less) responsive subgroups, dosing or duration of therapy. Likewise, clinical trials have not yet evaluated the role of infliximab in the post-surgical model of recurrence. Interleukin 10 has undergone a series of clinical trials in Crohn's disease without resounding clinical benefits. An, as yet, unpublished

Corresponding author : Hanauer S; B., University of Chicago Pritzker School of Medicine, Section of Gastroenterology, 5758, S. Maryland Ave, MC9028, Chicago, Illinios 60637, USA.

trial of interleukin 10 to prevent recurrence of Crohn's after resection apparently did not have positive outcomes. Thus, the post-surgical model offers a new realm for the development of biologic therapies that remains to be explored.

References

1. TARGAN S.R., HANAUER S.B., VAN DEVENTER S.J. *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N. Engl. J. Med.*, 1997, **337** (15) : 1029-1035.
2. RUTGEERTS P., D'HAENS G., TARGAN S. *et al.* Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology*, 1999, **117** (4) : 761-769.
3. PRESENT D.H., RUTGEERTS P., TARGAN S. *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N. Engl. J. Med.*, 1999, **340** (18) : 1398-1405.
4. D'HAENS G., VAN DEVENTER S., VAN HOGEZAND R. *et al.* Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease : A European multicenter trial. *Gastroenterology*, 1999, **116** (5) : 1029-1034.
5. BAERT F.J., D'HAENS G.R., PEETERS M. *et al.* Tumor necrosis factor alpha antibody (Infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology*, 1999, **116** (1) : 22-28.
6. D'HAENS G., SWIJSEN C., NOMAN M., LEMMENS L., GEBOES K., RUTGEERTS P. Etanercept (TNF receptor fusion protein, Enbrel) is effective and well tolerated in active refractory Crohn's disease : results of a single center pilot trial. *Gastroenterology*, 2000, **118** (4) : A656.
7. LOCHS H., MAYER M., FLEIG W.E. *et al.* Prophylaxis of postoperative relapse in Crohn's disease with mesalamine : European Cooperative Crohn's Disease Study VI. *Gastroenterology*, 2000, **118** (2) : 264-273.